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June 21, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Nos.: 92N-0258 and 88N-0258
Rule on 21 CFR Parts 203 and 205

Dear Sir or Madam:

This letter will serve to present the written comments of Droguería Central, Inc. ("DCI"), a small drug wholesaler, to the final rule recently issued by the Food and Drug Administration (FDA) relating to the wholesale distribution of prescription drugs.

Droguería Central's Business

Droguería Central, Inc. is a long established drug wholesaler on the island of Puerto Rico. While DCI is a closely held corporation (incorporated under the laws of the Commonwealth of Puerto Rico) and therefore doesn't publish its financial numbers, it sales on the island of Puerto Rico for its last fiscal year exceeded $130,000,000. We believe DCI is the second largest drug wholesaler on the island, behind Bergen Brunswig.

DCI's customers include pharmacies, hospitals, drug wholesalers, and other health care entities. These customers have come to depend upon DCI for a variety of quality products and services, and for the competitive prices and related benefits that DCI's presence in the market provides.

DCI purchases the bulk of the pharmaceuticals and medical supplies, which it distributes, directly from their manufacturers'. The relationship between DCI and these manufacturers is verbal. [1] DCI currently does not have written agreements with these manufacturers. However, for the last 15 years DCI each month has acquired, and the manufacturers have serviced without exception, millions of dollars of pharmaceutical products directly from them. It is thus readily apparent that these manufacturers consider DCI to be one of their primary clients in the island

[1] For a number of years, the manufacturers annually provided DCI with written supplier agreements; which DCI promptly executed. However, on or about 1994 the manufacturers discontinued mailing such written agreements to DCI or any other drug wholesaler in the island. This notwithstanding, the manufacturers have continued to supply pharmaceutical products to DCI without interruption, each year in ever growing volumes.

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and, as such, an authorized distributor of record as defined under the guidance issued by the FDA in August, 1988 with respect to prescription drug pedigrees and authorized distributors ("Guidance").

DCI is not a full line distributor and often purchases products from other wholesalers to meet its needs. All of these suppliers are licensed with the applicable state agencies where they do business. DCI purchases approximately 95% of the products it distributes directly from manufacturers. It purchases approximately 5% of the products it distributes from wholesalers. No wholesaler in Puerto Rico, and for that matter from the mainland, provide prescription drug pedigrees in connection with products for which they are authorized distributors (as that term is defined under the Guidance).

DCI operates out of a modern state of the art facility on the island of Puerto Rico. We employ 95 hard working men and women and provide them and their families with competitive wages and benefits. DCI is registered and licensed with various federal and commonwealth agencies including, the FDA, DEA, and Department of Health. Over the years, DCI's facilities and procedures have been regularly inspected and reviewed by these agencies. DCI has not been cited for any violations for a number of years.

While DCI welcomes any proposal by the FDA that will ensure its continued receipt of quality products and the continuing availability of safe drugs, it respectfully believes that the final regulations published in the Federal Register of December 3, 1999 (64 FR 67720, hereinafter referred to as the "Regulations") do not represent a positive evolution towards the attainment of these objectives. For these reasons, DCI politely submits these comments.

Impact of the Regulations on Wholesale Distribution

The Regulations, in an attempt to assure the safe storage and distribution of drugs and to assure a level of record maintenance that would allow for the tracing of the distribution chain of the drugs from manufacturer to consumer, grants the drug manufacturer the unhindered and unilateral authority to contractually designate those wholesalers to be deemed "authorized." (See, 21 CFR §§203.3(u) and 203.50) However, we believe that the FDA need not so empower the drug manufacturer in order to achieve these objectives. For example, the FDA could establish specific minimum standards which, once met, would deem a distributor as authorized to distribute prescription drugs. These would set standards for housekeeping, records and their retention, storage, and transportation and be much more specific than those contained in 21 CFR Part 205.50. Under this approach, the determination whether a distributor is deemed "authorized" would fall not on the hands of the manufacturers [2] but rightfully on the FDA and/or states.

[2] Indeed many manufacturers do not meet the FDA's standards (see Exhibit A).

If prescription drugs are distributed only through distributors which meet the specific minimum standards established by the FDA, then the safety and proper handling of these products through the distribution pipeline will be assured without further increasing the market leverage and power of drug manufactures and thus changing the balance and dynamics of the marketplace. If ever the government or law enforcement requires clear records of the distribution chain of any particular product, these are already available under the Regulations. In any event, any products purchased from a distributor who is not authorized should come with a written certification from such distributor that the drugs were first sold into the distribution system by or through an authorized distributor. This would allow for a precise map of the distribution chain.

It is necessary to point out that, as presently drafted, 21 CFR §§203.3(u) and 203.50 is particularly onerous to small drug wholesalers in the United States, and particularly to those in the island of Puerto Rico.

It is commonly known that drug distributors' net margins are low. [3] Yet the type of controls and the volume of paperwork required by the regulations would increase our administration costs, diminish the speed in our "just-in-time" systems and ultimately create a mass of paperwork which invariably ends filed in ever expanding file cabinets. The additional burden will add no more information than presently contained within DCI's records, [4] or those records of the drug wholesalers who supply DCI. In fact, the net effect of the rules will be to duplicate data which is already readily available in the systems of another distributor.

The compliance burden in all likelihood will result in the creation of a new department within our organization, without any additional revenues. Consider, for example, that DCI may have to provide documentation showing proof of the distribution chain (i) to each one of its clients (ii) each time a client purchases a drug from DCI. Note that DCI has over 670 customers (90% of which are decentralized independent businesses). Additionally, segregated records will have to be maintained on each item purchased from a distributor other than the item's manufacturer; this will, in addition to record keeping nightmare, require segregation of the inventory, so that purchase records match with sales records. In some cases the same products from the same lots and expiration dates will have to be segregated solely because of the record keeping requirements flowing directly as a result of the Regulations.

To contextualized our concerns, note that DCI invoices over 550 sales per day. Each invoice is separate and contains only those drugs sold to one of our 670 plus accounts In addition each invoice contains an average of 9 different drug products (in short, DCI handles approximately 5,000 products a day). Under current competitive forces in the island, the customers place multiple orders per week (average of 3 times per week) and expect same day

[3] DCI's net margins are below 1%.

[4] DCI's records meet the requirements set forth in 21 CFR Part 250.50(f).

delivery for all orders placed in the morning, and next morning delivery for all orders placed in the afternoon.

The Regulations, as presently proposed, would require that with respect to each one of the 550 orders invoiced each day by DCI, and with respect to the over 5,000 products packed in these orders, DCI must first determine which products in the order were purchased from a source other than the manufacturer and once this determination is made, it must include all the requisite paper trail so as to inform the client as required by the Regulation. It is apparent that such requirements are cumbersome and would have a negative impact on DCI's "just-in-time" delivery system; diminishing one of the few competitive advantages the small drug wholesalers have against the drug wholesale giants in the industry.

Thus compliance with this aspect of the Regulations represent a costly burden to DCI; multiply this effort and expense by the reported 4000 or so small drug distributors and the burden on the system is enormous. Query whether this burden is worth the cost? We believe that with the simple device of a letter or a phone call federal, state or local law enforcement can easily obtain the needed information;[5] avoiding in this manner imposing on DCI and small drug wholesalers the burdensome requirements presently contemplated in the Regulations.

Impact of the Regulations on Open Market Forces.

We believe that the FDA has good reason to concern itself with whether those handling the products comply with all applicable licensure requirements. In this context, any distributor who meets or exceeds the federal and state licensing standards for storage, handling, record keeping and transporting prescription drugs should be considered an authorized distributor of any manufacturer with whom it has an ongoing relationship.[6] Records of such transactions are already required to be kept by the distributor so as to allow the federal, state or local law authorities to effect any review or inspection deem necessary. This should be all that is required by PDMA.

However, the Regulations go beyond the establishment of a "security and tracking mechanism." In fact, as presently drafted, the Regulations provide to the manufacturers extraordinary leverage in their negotiations and dealings with drug wholesalers; particularly small drug wholesalers. Thus manufacturers that heretofore have done business with DCI may chose to use the new regulations to limit their distribution on the island to one preferred supplier (which, given the presence in Puerto Rico of Bergen Brunswig, a leading nation-wide drug

[5] Indeed 21 CFR Part 205.50 requires as a condition to being a licensed drug distributor that these records must be immediately available for inspection by federal, state and local law enforcement and inspectors.

[6] We believe that one or more transactions within one year should be sufficient to establish an ongoing relationship and that the existence of a written contractual agreement is not necessary as long as there exist a vendor-buyer relationship between the manufacturer and the wholesaler.

wholesaler, may not be DCI), to control sales and maintain high prices for its products. Alternatively they may use the regulations to impose new and onerous requirements on DCI and small drug wholesalers, or negotiate a higher contract price.

As a result, the Regulations venture into a territory that rightfully belongs in the private sector. Clearly, manufacturers can chose to whom they want to sell their goods.[7] However, the manufacturer should not be able to utilize the Regulations as a tool through which to control the downstream distribution of their goods. From this perspective, one needs to question whether the Regulations, as presently drafted and as may be leveraged by manufacturers against distributors, might violate current antitrust and trade regulation laws.

Limited Distribution Possess Serious Risks To The Marketplace

If in fact the Regulations have the unwanted result of transferring to the manufacturer control over downstream distribution, a manufacturer trying to maintain a monopoly or high prices on its products, even after its patents expire, would have ability to do so by limiting the distribution of its drugs to a few distributors. The wholesaler, in turn, would have no incentives to be price competitive, as a result of the manufacturer's limited distribution network, there would exist only limited competition exits, thereby allowing both manufacturer and the privileged distributor the ability to charge whatever the traffic will bear.

The current open marketplace permits transactions between distributors who are not authorized by the manufacturer to distribute those goods, however, the unauthorized distributors must, at a minimum, meet applicable state licensure laws and comply with the Guidelines. The fact that a distributor is not authorized by a manufacture to distribute its goods means nothing more than that it does not have an ongoing relationship with the manufacturer. There is nothing in the records that indicates that these unauthorized distributors do not comply with the requirements of 21 CFR Part 205 or state and local laws.

Furthermore, and as the Small Business Administration has already pointed out, the regulations will devastate thousands of small business, the majority are closely held family businesses, many owned by minorities. It would be unfortunate if one of the by products of the Regulations is the decimation of many of the 4,000 small and minority drug distributors currently active in the nation; reducing that amount to a few alarmingly large ones.

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[7] It should be noted that the bulk of the manufacturers are billion dollar plus companies with sophisticate staffs dedicated to maintaining market share and profits. These multi-billion dollar manufacturers are not in need of any assistance from FDA in preserving their market share or defining with whom they do business. On the other hand, the bulk of the 4,000 drug distributors are small business that stand the risk of being eliminated from the distribution chain as a direct result of the Regulations. It is worthy of notice that these businesses already comply with existing federal and state licensing requirements.

Lastly, we believe that the prescription drug pedigree requirement inhibits competition because, through these pedigrees, suppliers and customers, will become known to the downstream buyers. This information is highly sensitive, confidential and guarded within a distributors company. Under state law this information is deemed to be trade secret.

The statute and the regulations force this information to be disclosed whenever the distributor sells a product which was not originally acquired directly from the manufacturer. This places a distributor's business in jeopardy for its most sensitive business information is forced to be disclosed to its client and, perhaps through the latter, to its competitors.

A distributor meeting federal and state licensing standards for housekeeping, storage, handling, record keeping and transportation should be deemed "authorized" for all intents and purposes. In such manner, the highly sensitive business information of the distributor will remain protected from disclosure to all except the FDA and to federal, state or local law enforcement or inspectors (who, by law, are required to maintain the privacy of this information, except for their own use). As a result, a significant portion of the "business goodwill" of a drug distributor is protected; all the while minimizing disruption in the industry.

Conclusion

In summary, we respectfully request that the FDA re-evaluate and change in accordance with the views presented herein those elements in the Regulations dealing with the "paper trail" requirements and the definitions of "authorized distributor" and "ongoing relationship." As these stand today, they will dramatically change the distribution dynamics and shift the control of drug distribution exclusively to the manufacturers and a few large wholesale distributors (which today already control 90 percent of the marketplace). Thus we believe both, that (i) there is no compelling reason for these elements of the Regulations and (ii) the burden and cost of these elements far outweigh any benefit they may provide.

The fact is that just because a distributor does not purchase a drug directly from a manufacturer does not and should not *de facto* mean they are a second-class distributor or that the products are likely to be adulterated. Unfortunately, it seems that this erroneous and highly prejudicial assumption forms the basis for the Regulations.

Thus we urge the adoption of a far simpler, and efficient, model: ***any distributor that meets or exceeds the FDA's (and states) standards for storage, handling, record keeping and transportation should be able to distribute any drug it deems appropriate to meet its business requirements; whether acquired from manufacturers or other licensed distributors.***

In conclusion, and in further support of the views in opposition to the rules as expressed by many others, [8] we hope that the FDA will carefully and thoughtfully consider our concerns and take them into account in crafting a rule that will preserve the drug distribution system in our country without increasing our costs or otherwise imposing exclusively upon manufacturers the ability to control the destiny of our business.

For the foregoing reasons, DCI respectfully requests that the Regulations be revised to conform, at a minimum to the Guidelines.

Please call with your questions.

Very truly yours,

DROGUERIA CENTRAL, INC.

Guillermo I. Marrero - Rivera
President

[8] Among these, the National Wholesale Druggists' Association, National Association of Chain Drug Stores, Food Marketing Institute, American Veterinary Distributors Association, National Community Pharmacists Association, Health Industry Distributors Association, U.S. Small Business Administration, American Red Cross, American Blood Centers, Pharmaceutical Distributors Association and Ukrop's Super Markets, Inc., etc.

EXHIBIT A

DEPARTMENT OF HEALTH & HUMAN SERVICES

HFI-35

Public Health Service
Food and Drug Administration

m1340m

Dallas District
3310 Live Oak Street
Dallas, Texas 75204-6191

February 7, 2000

WARNING LETTER

Ref: 2000-DAL-WL-04

VIA FEDERAL EXPRESS

Mr. Miles D. White
Chief Executive Officer;
Chairman of the Board of Directors
Abbott Laboratories, Inc.
100 Abbott Park Road
Abbott Park, IL 60064-6092

Dear Mr. White:

During an inspection of your medical device manufacturing facility located in Irving, Texas, from 10/26/99 to 12/22/99, our investigators determined your establishment manufactures clinical chemistry analyzers. Clinical chemistry analyzers are devices as defined by Section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act).

The above-stated inspection revealed these devices are adulterated within the meaning of Section 501(h) of the Act, in that the methods used in, or the facilities or controls used for manufacturing, packing, storage, or installation are not in conformance with the Quality System/Good Manufacturing Practice (QS/GMP) Regulation as specified in Title 21, Code of Federal Regulations (CFR), Part 820, as follows:

1. Failure to appropriately document and or investigate incidents of nonconformance to the depth necessary to correct and prevent problems from recurring [21 CFR 820.90 (a)]. Specifically,

   Failure to enter nonconformances into the NCR database which is used to record and monitor nonconformances. For example during the period from 3/17/99 to 8/25/99, [redacted] nonconformances were not entered into the NCR database e.g. NCR #[redacted]

2. Failure to establish and maintain procedures needed to correct and prevent the recurrence of nonconforming product and other quality problems [21 CFR 820.100(a)(3)]. For example,

The Corrective and Preventive Action Procedure (DA-01 ADD Dallas Quality System Manual) fails to identify the procedures to be used for identifying and tracking software related complaints.

The practice of "closing" uncorrected software and/or instrument problem reports against one version of software and renumbering them for possible correction in a subsequent version of the software is not described in the CAPA procedures.

Failure investigation for Alcyon S/N [redacted] was not performed for customer complaint involving unresolved DIV errors, sample and ion specific electrode (ISE) arm crashes, and burning smell. The risk assessment concluded there was no risk to the operator or patient because the instrument was not longer in the possession of the customer. A thorough investigation was not done to identify other problems that could be inherent in all similar products.

Failure investigation for Alcyon S/N [redacted] noted the device locked-up in the middle of a run. There is no investigative information regarding the actual use conditions of the device at the time of the lock-up.

Failure investigation for Alcyon S/N [redacted] showed repetitive attempts at correcting the problem in the field by replacing the ISE module and tubing, only to have additional complaints for the same problem. The in-house failure investigation repeated the same field action of replacing the ISE module and tubing and concluded the problem was solved. No further investigation was made to determine why previous corrective actions with the replacement of the ISE module and tubing were not effective.

3. The Corrective and Preventative Action (CAPA) Procedures failed to analyze all sources of quality data to identify existing and potential causes of nonconforming product or other quality problems [21 CFR 820.100(a)(1)]. For example,

   Nonconformance data from printed circuit boards returned from field service, non-conforming components and processing defects such as solder joint failures are not compiled and analyzed for trends.

   Failure to investigate the cause for [redacted] Alcyon devices failing the accuracy and precision tests during finished device testing during the period from March 10, 1999 to November 11, 1999.

4. Failure to establish and maintain procedures that will verify the effectiveness of corrective and preventive action(s) taken [21 CFR 820.100(a)(4)]. For example,

   There are numerous unresolved hardware and software reliability problems associated with the Alcyon Analyzer. Problems including known system lock-up and system reliability issues were identified prior to the release of software version 1.0 in April 1998. Some of these problems still exist and additional

reliability problems have since been identified and remain uncorrected in the current software version 1.5. There are no plans to address these problems with the corrective actions to be implemented with software version 1.8, proposed for release in July 2000.

Test Process Change Notice #4170 dated 10/8/99 directed a change involving component (U29) was incorrectly identified as U9. The change was reviewed, approved and implemented without the error being detected.

System Problem Reports identified under DAL[redacted] covered several lock-up problems and failed to provide sufficient information to determine if a software revision introduced a new lock-up problem or if the specific lock-up problem was in a pre-existing version of the software.

5. Failure to document all activities and results required for the corrective and preventive action system [21 CFR 820.100 (b)]. For example,

   There is no assurance all complaints involving software defects are recorded in a software problem report. A System Problem Report was not generated for [redacted] ticket #[redacted] dated 5/15/99 involving an AxSYM software error.

   There is no assurance software problem reports are accurately associated with the correct version of software. For example, in AxSYM SPR DAL-[redacted] the field for affected version references version 3.04; however, the narrative in the detailed problem description references version 3.60.

   System Problem Reports for the Alcyon devices do not always show an instrument serial number or complaint ticket number so that the SPR can be traced to the original field complaint. On occasion, this information is recorded in the memo text field of the report, which is not easily extracted.

6. Failure to establish and maintain procedures to ensure the design requirements relating to the Alcyon software are appropriate and address the intended use including user needs [21 CFR 820.30(c)]. Specifically, neither the ADD Software Development Requirements nor the Product Version Description Document (PVDD) for the Alcyon software version 1.5 make reference to any boundary condition(s) such as minimum, maximum or normal number of tests the Alcyon device is designed to perform within a given time period. Additionally, the PVDD for software version 1.7 contains no documentation showing that user needs have been addressed in the current software revision 1.5 or the next software version (1.8) as evidenced by over [redacted] open enhancement system problem reports.

7. Failure to establish and maintain procedures that verify and document that the design output conforms to design input requirements and that the design outputs were documented, reviewed and approved prior to release [21 CFR 820.30 (f)]. Specifically,

The Verification and Validation Test Protocol (#[redacted]), used in the testing of software versions 1.6 and 1.7, did not define the number of repetitions to be used in the performance of the stress test, the boundary conditions for volume and load, and the criteria used to accept the test results.

The PVDD Version 1, Alcyon rev 1.5 showed over [redacted] open System Problem Reports (SPRs) at the time of its release in November 1998.

The PVDD, Version 2, Alcyon rev.1.0 for software version 1.7 showed open SPRs which had been identified as software problems during the testing of versions 1.0 through 1.5, e.g. DAL[redacted] and DAL [redacted]

8. Failure to establish and maintain procedures for the documentation, verification, review and approval of design changes before their implementation [21 CFR 820.30(i)]. For example,

   Engineering Change Process procedure No. DA-04, Rev. K, dated 6/28/99, used for post-production changes did not have provisions for addressing pre-production change control and risk analysis.

   ECN [redacted] dated 10/12/99, Software version 1.5, which was under development, was used in design verification and validation when the protocol specified that version 1.02 was to be used. There was no documented protocol approval of this design change prior to its implementation.

9. Failure to fully validate the Surface Mount Technology process used in the production of printed circuit boards (PCBs) in that the data from only [redacted] boards from [redacted] run were used. Evaluation of temperature profile effects on temperature sensitive components, solder paste application and other production variables were not included or were not equivalent to a full production run [21 CFR 820.75(a)].

10. Failure to establish and maintain acceptance procedures to ensure that PCBs processed on the Surface Mount Technology line meet specified requirements [21 CFR 820.80 (c)].

11. Failure to establish and maintain finished device acceptance procedures that ensure that finished devices meet acceptance criteria [21 CFR 820.80(d)]. Specifically, Alcyon S/Ns [redacted] and [redacted] were released with incorrect values for the A-PNA Extinction Factor, which resulted in the failure of each unit to meet the Gamma-Glutamyl Transferase assay specification.

This letter is not intended to be an all-inclusive list of the deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and regulations. The specific violations noted in this letter and in the FDA-483 (copy enclosed) issued at the conclusion of the inspection to Mr. Jorge F. Artiles, Quality Assurance and Regulatory

Affairs Manager, Abbott Laboratories, Diagnostic Division, Irving, Texas, may be symptomatic of serious underlying problems in your establishment's manufacturing, quality assurance and/or quality management systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. If the causes are determined to be system problems, you must initiate actions that will permanently correct the root causes of the problems.

Until these violations are corrected, and FDA has documentation to establish that such corrections have been made, federal agencies will be advised of the issuance of this Warning Letter so that they may consider this information when considering the award of contracts.

We have received and reviewed your letter, dated January 14, 2000, in response to our inspectional findings. In general, we find it inadequate. Your response lacks supporting evidence and in some instances, fails to address underlying issues that may have contributed to or resulted in the deficiencies. We are also concerned over the proposed time frame for implementing some of the corrections. Some of our concerns are:

Observations 1, 6: We are not convinced that the use of a simulator to run worst case scenarios will identify all the conditions contributing or leading to the system lock-ups. Use of a simulator requires the input of known conditions or variables and may not consider conditions that may exist in real time use. The use of a simulator alone is not a substitute for full and complete validation of the software. Please explain how you plan to handle unresolved hardware and software problems.

Observation 2: Although the SOP (Q04.02, ADD Software Development Process) may correct the problem, we remind you that is should incorporate the consideration of user needs which may or may not be completely identified through a review of the SPRs. Please explain if this procedure is to be implemented division-wide. If not, why? Please provide an explanation as to why it will require nearly 3 months to implement the SPR Review Procedure.

Observation 7: Although you reference several existing procedures which address the soldering process of printed circuit boards, your response contains no evidence that the procedures employ an effective quality control program over the process. Solder joints are not something that can be tested with automated circuit testers since a number of bad solder joints such as insufficient solder, lack of or insufficient heat, cracked joints, and contaminated joints will pass electrical tests. We wish to point out that your own trending data identified solder joint failures as a problem. This problem arose under the current quality program. Therefore, we find your response unacceptable. We note in the response a reference to an Attachment #5 that was not provided.

Observation #8: In your response to item 8.a., you state you will develop a new SOP to address the tracking of software failure investigations and will implement this procedure by May 31, 2000. Please provide an explanation as to why it will require nearly 3 months more to implement the procedure.

In your response to item 8.b., you state that all open SPRs will be reviewed for inclusion in the Alcyon version 1.8. We remind you that the larger issue is the handling of all SPRs. The underlying problem(s) are not limited to the Alcyon device.

Observation 12: We find your response unacceptable. Your response fails to provide any documentation showing the soldering processes, particularly the paste application and component placement, have been properly validated. Possible underlying issues that need to be addressed include how your firm approved the validation protocol and data when the testing wasn't representative of the process over time. We also note in your response a reference to Attachment #6, a 1996 validation package for the [redacted] Oven. This document was not included in attachments provided.

Observation 13: You identify several steps you plan to take to identify the root cause of the lock-up problems. We believe you are negating the most vital source of information, that obtained directly from the user. Although you indicate you will review the SPRs, we remind you that during our inspection, our investigators noted that many of the SPRs lacked basic information concerning the conditions leading or contributing to the problem. Failure to obtain this data raises questions on the reliability of the action(s) you might take to correct the lock-up problem(s).

Observation 14: Your response to item 14.a. does not address the underlying issue of what led to the issuance and approval of an SOP that would permit non-conformances to go uninvestigated or partially investigated. Additionally, issuing a new procedure is only part of the solution. Please provide an explanation as to how you plan to monitor and evaluate adherence to the new SOP i.e., Q14.03.

In your response to item 14.b., you state you will issue a Quality Directive that will detail the information customer service representatives need to obtain for a thorough evaluation of the system lock-ups. Please provide an explanation as to how this directive will fit into the CAPA system.

We find your response to item 14.e. inadequate. You state the service manual addresses the failure mode of the ISE module and consequently no further action is necessary. We disagree. Please provide an explanation as to why the field service technician(s) and the in-house investigator(s) tried to resolve the problem by replacing the ISE module and related tubing on several occasions instead of recognizing the problem as specified in the service manual. Please explain why the investigation was closed when the only apparent solution was to replace the ISE module without having determined the root cause of the problem. Identify the steps you plan to take to prevent the recurrence of this kind of performance and your plans to monitor and evaluate adherence to the corrective action plan.

Observation 15: You state that a new CAPA procedure will issue to add consistency to the problem tracking and resolution processes. Underlying issues that need to be investigated include variables contributing to the lack of consistency e.g., employee understanding of the SOP, clarity of the SOP, outside influences (such as time, resources), etc. Please specify how the SOP will accomplish this goal and how it will address the practice of closing SPRs and renumbering them against future software revisions. Include in your explanation the measures you plan to take to monitor and evaluate adherence to the new SOP.

Observation 18: Provide an explanation as to how the ADD division instrument system problem reporting process procedure will achieve consistency in the tracking and resolution of problem reports and how it will change the practice of employees ignoring or circumventing valid SOP's without documentation. Also explain if the procedure will be implemented division-wide and what measures you plan to take to monitor and evaluate employee adherence to this new SOP and others e.g. OP-DA-04, Engineering Change Process.

Your response to observations 18.b.i and ii. is unacceptable. You state that the process change (ECN) was written, reviewed and approved with the incorrect information on the ECN. You do not address how the ECN cleared the approval process with the incorrect information or without documented justification of the error or the manner in which the ECN was ultimately handled. Please provide an explanation of the measures you plan to take to prevent the recurrence of the procedural failures.

Similarly, in your discussion of the actions you plan to take to correct the problems identified in observation 18.c., you indicate you will implement a new procedure or change existing procedure(s). Although the SOP(s) may need changing, your response does not address the underlying issue of why the original procedure was not followed and how you plan to monitor and evaluate adherence to the new procedure(s).

Observation #19: Please explain if the new procedure for the technical design review (OP-DA-27) will be a division-wide procedure. If not, explain why the procedure needs to be different from the Lake County procedure and how it relates to OP.J207.

Observation 20: Your response is not acceptable. Although you provided data showing the error posed no clinical significance, you failed to address the cause of the problem(s) and what steps you will take to prevent its recurrence. Furthermore, your response only mentions the fact that several finished devices ([redacted] by your count) were released for distribution that failed to meet a finished product test specification. We wish an explanation as to how this situation could be undetected for nearly a year.

Observation 24: We note in your response that your investigation into the cause of the failures of the ratio dispense tests for accuracy and precision will be completed by March 31, 2000. Yet you state the [redacted] instruments that failed this test specification during the period from 3/10/99 to 11/11/99 were corrected prior to release. If the investigation is still ongoing (not complete), please provide a detailed explanation as to what assurances you have that the [redacted] units were properly fixed prior to release and the step(s) you plan to take to prevent the recurrence of this situation.

You also state that a Dallas site standard for root cause analysis will be implemented. Explain if this standard will be effective division-wide and if not, why.

Observation 25: Although you state you will clarify the instructions to improve the coding process to be used to categorize non-conformances by part number, we question whether this action alone will achieve the desired improvement. Please explain how the new instructions will ensure consistency in the coding process and your plan to monitor and evaluate adherence to the procedure. If the Dallas site standard for trending is applicable

only to the Dallas site, please explain why it shouldn't apply division-wide. Additionally, we note in your response that a [redacted] by part number is included among the assessments tools used to trend non-conformances. We question the reliability of this information given the inconsistencies in the categorization process that was sited as a deficiency.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to seizure, injunction, and/or civil penalties.

Please notify this office in writing within 15 working days of receipt of this letter, of the specific steps you have taken to correct and prevent the noted violations and to address our concerns. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to John W. Thorsky, Acting Compliance Officer, Food and Drug Administration, 1445 North Loop West, Suite 420, Houston, TX 77008.

Finally, we acknowledge receipt of and concurrence with your company's decision to recall the Alcyon 300/300i from the United States market place. However, we remain deeply concerned that these deviations may impact other devices made at the Irving, Texas facility and those Alcyon devices that will be marketed in foreign countries. We remind you of your commitment given to this agency on 12/22/99 not to distribute any of the Alcyon 300/300I devices until the software problems have been corrected and FDA approval of software version 1.8 has been obtained.

Sincerely,

Michael A. Chappell
District Director
Dallas District

Enclosure-FDA-483

cc: Mr. Thomas D. Brown, President
Diagnostic Division
Abbott Laboratories, Inc.
100 Abbott Park Road
Abbott Park, IL 60064

Ms. Cecilla Kimberlin
Division Vice President
Regulatory Affairs, Compliance and Audits
Abbott Diagnostic Division
Abbott Laboratories Inc.
D-9Y6, Building AP6C
100 Abbott Park Road
Abbott Park, IL 60064-6092

Ms. Diane H. Brunson
Division Vice President for Instrument Manufacturing
and Dallas Site Operations
Abbott Laboratories, Inc.
1921 Hurd Drive
Irving, TX 75038

DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT
Madden

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

WARNING LETTER

September 28, 1999

99-PHI-36

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Bernard J. Poussot, President
Wyeth-Ayerst Laboratories
Division of American Home Products Corporation
555 East Lancaster Avenue
St. Davids, PA 19087

Dear Mr. Poussot:

The agency has completed its review of the results of an inspection conducted at your West Chester, PA drug manufacturing facility from March 8 through May 5, 1999 by Philadelphia District Investigators Michael D. O'Meara and David J. Hafner and Northeast Regional Laboratory Pharmaceutical Microbiologist Dennis E. Guilfoyle, Ph.D. The inspection documented significant deviations from current Good Manufacturing Practice (cGMP), *Title 21 Code of Federal Regulations* (21 CFR) Parts 210 and 211, with respect to the manufacture of certain lots of epinephrine injection and meperidine HCl injection. At the conclusion of the inspection, the inspectional team issued form FDA 483, Inspectional Observations, to Robert R. Shemonsky, Managing Director. A copy of the FDA 483 is enclosed for your information.

These deviations cause certain lots of epinephrine injection and meperidine HCl injection, manufactured at this facility, to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) since the methods used in, or the facilities or controls used for, their manufacture were not operated or administered in conformity with cGMP, as follows:

1. Failure to assure that drug products meet all of their applicable quality standards throughout their labeled expiration date.

The inspection revealed that stability and retained samples of some lots of epinephrine injection, USP, contain individual Tubex syringe units that have become discolored over time such that they fail to meet your firm's stability specification for physical description which requires, in part, a "clear, colorless solution." Current good manufacturing practice requires that drug products meet all of their appropriate quality standards throughout their shelf life. Your firm has identified physical description as a quality standard, and your firm's data indicate that product older than 25 months does not consistently meet this quality standard. The caution against using discolored product that is contained in the product labeling does not provide an adequate remedy

since product older than 25 months may not meet its quality standard for physical description. Your firm's investigation into this matter found individual Tubex syringes of epinephrine, approximately 25 months of age or older, that failed to meet your firm's in-house [redacted] limit. In May 1998, Wyeth-Ayerst Laboratories (Wyeth) shortened the expiration date for epinephrine injection from 30 months to 24 months, and post-inspectional correspondence from Wyeth states that this action was taken to decrease the potential for discoloration in individual units. This decision did not, at that time, impact on commercially distributed product already labeled with the 30 month expiry date.

We acknowledge your firm's recent decision to voluntarily recall lots of epinephrine with the 30 month expiry date. However, your firm has not, to date, identified the chromophore causing the discoloration. We note that lots of epinephrine injection produced at West Chester appear to exhibit a more significant discoloration pattern than either the three lots manufactured to support the transfer of manufacturing operations for this drug from your Marietta, PA facility to the West Chester site, or the control lot produced at Marietta against which the three lots were compared.

The USP color and clarity test is included in your firm's stability testing specification for epinephrine injection; however, discolored units have not been subjected to this test. Rather, these units have been evaluated using your firm's in-house [redacted] test. This test has not been proven to be equivalent or superior to the USP test although we note your firm's opinion that the [redacted] test is superior to the USP color and clarity test.

2. Failure to assure that the system used to clean and disinfect processing areas in which sterile drug products. particularly epinephrine injection lot [redacted] and meperidine HCl injection lot [redacted] are filled consistently returns the rooms and equipment to aseptic conditions.

Your firm's investigations into failures of two media fill trials run on August 2, 1998 and September 28, 1998 identify inadequate disinfection and failure to remove a contaminated machine cover at the appropriate sequence in the disinfection process as the most likely causes of the failures.

Post-inspectional correspondence indicates that a sporicidal disinfectant was applied to and a routine disinfection performed in the applicable sterile areas prior to filling epinephrine lot [redacted] on September 21, 1998. During our inspection, review of the available cleaning and disinfection documentation for the filling equipment revealed that the "Hopper, Bowls, Rails" were disinfected [redacted] with [redacted] about [redacted] prior to the start of the fill. In contrast, available documentation for the filling equipment cleaning and disinfection done prior to the two failed media fills shows that the hopper, rails, and bowls were disinfected [redacted] with [redacted] prior to the start of the respective fills. Post-inspectional correspondence from your firm reports that the room equipment disinfection logbook documents that equipment disinfection was

performed in accordance with your written procedures. However, this logbook does not document that all of the machine parts and surfaces listed in the applicable procedures were disinfected or that the parts were disinfected in the required sequence. Your firm's correspondence also states that no action or alert levels for microbiological monitoring of air, surfaces, and personnel were exceeded during filling; our review of the applicable records found that no action levels for routine microbiological monitoring of air, surfaces, and personnel were exceeded during filling of the two failed media fills.

We have similar observations regarding filling of meperidine HCl lo[redacted] In summary, your disinfection procedures and/or the manner in which you adhere to them were not sufficient to preclude the media fill failures that occurred and, by extension, call into question the assurance of sterility for epinephrine injection lot[redacted] and meperidine HCl injection lot [redacted]

You should be aware that this is not the first time we have raised concerns about recovery from non-sterile conditions to the attention of Wyeth management. An inspection conducted July 1 through August 9, 1996 documented the post-disinfection presence of microbial counts of greater than [redacted] CFU/plate on the floor of the aseptic corridor and on the floor inside the doorway to one of the sterile filling rooms.

3. Failure to thoroughly investigate exceeded environmental monitoring action levels in the sterile filling room in which meperidine HCl injection lot[redacted] was filled.

The inspection revealed that your firm's environmental monitoring found mold, [redacted] species, on the floor which exceeded your firm's action levels for that surface. Post-inspectional correspondence from your firm states that the exceeded action levels were associated with environmental sampling conducted prior to filling the meperidine HCl and that floor samples taken during filling were negative for growth. However, documentation for samples taken during filling shows that the areas where positive growth was found prior to filling (south, east, west, and center floors) were not sampled. There is no documentation that additional disinfection was done between samplings.

Although your firm believes that these floor counts did not impact the aseptic filling operations because of negative environmental monitoring results for critical surfaces, personnel, and air, such monitoring cannot provide a complete overview of the room conditions. Our review of the literature found that [redacted] spp. can contaminate water damaged, cellulose-containing building materials. The literature reports it can be an opportunistic pathogen in immunocompromised individuals and references a 1988 incident regarding [redacted] spp. contamination of the air system and the HEPA filters in a hospital's oncology-hematology

special care unit. Four bone marrow transplant recipients were subsequently infected.[1] We note that the West Chester facility has had water leaks above the ceilings in the sterile core, has had periodic breaks in sterile conditions (to change HEPA filters or otherwise access ceilings), and has identified the presence of [redacted] spp. as part of a trend in the sterile environment between [redacted] and [redacted] Given that mold spores can become aerosolized, we have concerns regarding the source of the contamination. If it is above the sterile core ceilings, there is a potential for impact to the critical surfaces.

Your firm maintains that a ceiling or HEPA filter route of contamination is not likely because air and surface monitoring, with the exception of the floors, have been negative for [redacted] spp. contamination. We have not, to date, received any information from your firm regarding any investigation into possible contamination in the ceilings and/or HEPA filters or other potential source of this mold. We believe that cGMP requires additional vigilance in this area.

We have received and reviewed a letter dated May 25, 1999 from Mr. Shemonsky and Gerry Morris, Ph.D., Associate Director of West Chester Quality Assurance, which responds to the FDA 483 observations. We also met with Dr. Morris and other representatives from both Wyeth and American Home Products Corporation on June 9, 1999 regarding the inspectional findings. In additon, we had a second meeting with Mr. Shemonsky, Dr. Morris, and other Wyeth personnel on July 28, 1999 and are in receipt of a letter dated August 13, 1999 from Mr. Shemonsky regarding the status of your firm's corrective action commitments. As indicated above, these actions do not satisfactorily address all of the observations. We also have the following comments with respect to Mr. Shemonsky and Dr. Morris' responses to the following FDA 483 observations:

FDA 483 Observation 5.a.

The second paragraph of the response to this observation indicates that additional disinfection is performed prior to media fills that are conducted following a recovery from non-sterile conditions. As we pointed out during the June 9 meeting, it appears that this additional disinfection is not performed prior to filling the first lot of product following recovery from non-sterile conditions, which is a source of concern. The last sentence of that paragraph states that disinfection routines for media fills are designed to be equivalent to those for product; please clarify whether or not this will also pertain to disinfection routines employed following recovery from non-sterile conditions.

[redacted]

FDA 483 Observation 5.c.

On two occasions during the time period noted in the FDA 483 observation, the vacuum levels resulted in less than half the intended volume of air [redacted] cubic feet on March 6, 1998 and [redacted] cubic feet on March 9, 1998). Did these air volumes also result in a quantitative measure?

FDA 483 Observation 8

As mentioned previously, no environmental monitoring action levels were exceeded during filling of the two failed media fill trials. While environmental data are important, emphasis must also be placed on ensuring that your firm's procedures for recovering from non-sterile conditions consistently render the rooms and equipment suitable for aseptic processing regardless of the operations that require the break in sterility.

The above is not intended to be an all-inclusive list of deficiencies at your firm. As top management, it is your responsibility to assure that all of your company's operations are in compliance with the Act and its applicable regulations.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts. In addition, pending new drug applications (NDAs), abbreviated new drug applications (ANDAs), or export approval requests may not be approved until the aforementioned deviations are corrected.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include, but are not limited to, seizure and/or injunction.

Please advise this office in writing within fifteen (15) days of receipt of this letter as to the specific actions you have taken or intend to take to correct these violations, including an explanation of each step being taken to prevent recurrence of similar violations. Your response should specifically address any actions you intend to take with respect to epinephrine injection lot [redacted] and meperidine HCl injection lots [redacted] and [redacted] If corrective action cannot be completed within 15 days, state the reason for the delay and the time within which corrections will be completed. Your reply should be addressed to Karyn M. Campbell, Compliance Officer, at the address noted on the letterhead.

Sincerely,

Thomas D. Gardine

Thomas D. Gardine
District Director

U.S. Food and Drug Administration

FOIA WARNING LETTERS SEARCH

Matters described in FDA warning letters may have been subject to subsequent interaction between FDA and the recipient of the letter that may have changed the regulatory status of the issues discussed in the letter. If you wish to obtain available additional information on the current status of an issue in a particular warning letter or notice of violation on this website, please contact the Agency or the recipient of the letter directly. Inquiries to FDA should be sent to: Food and Drug Administration Freedom of Information Staff (HFI-35), 5600 Fishers Lane, Rockville, MD 20857. Instructions for how to submit an FOI request can be found at http://www.fda.gov/opacom/backgrounders/foiahand.html.

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Guy & O'Neill, Inc.	4/02/99	Minneapolis District Office	Good Manufacturing Practices Violations	View File
Health Science Laboratories and Services, Inc.	4/26/99	New Jersey District Office	Good Manufacturing Practices Violations	View File
Labtician Ophthalmics	12/18/98	Center for Devices and Radiological Health	Good Manufacturing Practices Violations	View File
LSG Lufthansa Service/Sky Chefs	10/23/98	San Francisco District Office	Good Manufacturing Practices Violations	View File
Pro Chemicals, Inc.	4/12/99	Minneapolis District Office	Good Manufacturing Practices Violations	View File
Seatrace Pharmaceuticals, Inc.	4/26/99	Nashville District Office	Good Manufacturing Practices Violations	View File
Signature Pharmaceuticals, Inc.	4/09/99	New York District Office	Good Manufacturing Practices Violations	View File
Bio-Pharm, Inc.	8/10/99	Philadelphia District Office	Good Manufacturing Practices/Drug Products Manufactured	View File
Wyeth-Ayerst Laboratories	9/28/99	Philadelphia District Office	Good Manufacturing Practices/Epinphrine and Meperidine HCl injections	View File
Sky Chefs/Lufthansa, Inc.	4/04/00	San Francisco District Office	Good Manufacturing Practices/Food & Beverage Services	View File
Rainbow Sprouts	8/26/99	Denver District Office	Good Manufacturing Practices/Sprout Growing Facility	View File

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Last Updated on 6/01/2000

U.S. Food and Drug Administration

FOIA WARNING LETTERS SEARCH

Matters described in FDA warning letters may have been subject to subsequent interaction between FDA and the recipient of the letter that may have changed the regulatory status of the issues discussed in the letter. If you wish to obtain available additional information on the current status of an issue in a particular warning letter or notice of violation on this website, please contact the Agency or the recipient of the letter directly. Inquiries to FDA should be sent to: Food and Drug Administration Freedom of Information Staff (HFI-35), 5600 Fishers Lane, Rockville, MD 20857. Instructions for how to submit an FOI request can be found at http://www.fda.gov/opacom/backgrounders/foiahand.html.

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Company Name	Date Issued	Issuing Office	Subject	File
Praxair Distribution, Inc.	11/03/99	Kansas City District Office	Gas Transfilling Operation/Liquid Nitrogen	View File
Advanced Athletic Nutrition	1/27/99	San Francisco District Office	GBL (Gamma-Butyrolactone)	View File
Alpha Earth, Inc.	1/27/99	Atlanta District Office	GBL (Gamma-Butyrolactone)	View File
Dailey, William H., Esq.	1/27/99	Florida District Office	GBL (Gamma-Butyrolactone)	View File
Miracle Marketing Distributors	1/27/99	Florida District Office	GBL (Gamma-Butyrolactone)	View File
RenewTrient Research	1/27/99	Florida District Office	GBL (Gamma-Butyrolactone)	View File
Institute for Human Gene Therapy	3/03/00	Center for Biologics Evaluation and Research	Gene Therapy	View File
Mikart, Inc.	1/16/97	Atlanta District Office	Generic Drug Products	View File
Satelec - Amadent	4/12/00	Center for Devices and Radiological Health	Glass Bead Dry Heat Sterilizer/Lacks Premarket Approval	View File
American Health Foundation	6/06/97	Center for Drug Evaluation and Research	GLP	View File
Idexx Veterinary Services, Inc.	8/27/97	Center for Drug Evaluation and Research	GLP	View File

CERTIFIED MAIL

7000 0520 0015 9127 8531

Drogueria Central, Inc.
P.O. Box 1366
Dorado, P.R. 00646-1366

RETURN RECEIPT REQUESTED

ROM:

ERV: CER

RK#: 700005200015912785

08/30/00 11:21

TO: HFA-305

OF PCS: 1

7182014091554

RM: HFA-305

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Drogueria Central, Inc.
P.O. Box 1366
Dorado, P.R. 00646-1366

CERTIFIED MAIL

7000 0520 0015 9127 8531

RETURN RECEIPT REQUESTED

FROM:

SERV: CER

TRK#: 700005200015912785

06/30/00
11:21

TO: HFA-305

OF PCS: 1

7182014091554

RM: HFA-305

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852